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Nanomaterial Mediated Drug Delivery, Image-Guided Therapy and Multifaceted Theranostic Systems in Cancer

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Abstract: Nanotechnology is the continuous expansion in the domain of engineered devices at the atomic, molecular and macromolecular level in nanometer range. Nanoparticles have prospective implication in medical field including diagnostics and therapeutics. Cancer is one of the foremost reasons of death worldwide. In 2013, a total of 1,660,290 new cancer cases and 580,350 cancer deaths are projected to occur in the United States alone. The total cancer cases can possibly go up from 979,786 cases in the year 2010 to 1,148,757 cases in the year 2020 in India. Nanotechnology devices are nowadays being established for diagnosis of cancer as well as infectious diseases which in turn can aid in early unveiling of disease.

This article explores progress in nanotechnology that have initiated the development of multifunctional platforms for cancer detection, therapy, and monitoring. Multifunctional nanomaterials can be utilized as drug carriers enhancing tumor uptake through the EPR effect as well as receptor-mediated endocytosis and on the other hand as MRI, optical imaging, and photoacoustic imaging contrast agents. Furthermore, imaging and therapy agents can be co-delivered to endow with flawless amalgamation of diagnostics, therapy and follow-up, and diverse therapeutic modalities like chemotherapy and hyperthermia can be co-administered to acquire benefit of synergistic effects. However, an intensive scientific endeavor is so far needed to entirely investigate long-term risks, effects, and precautions for safe human utilization.

Keywords: Nanotechnology, Targeted therapy, Drug delivery, Theranostics, Image-guided therapy.

1. INTRODUCTION

Nanotechnology (derived from the Greek word nano meaning dwarf) deals with the interactions of cellular and molecular components and engineered materials-characteristically, clusters of atoms, molecules, and molecular fragments into exceptionally small particles ranges between 1 and 100 nm [1, 2]. The potential for nanotechnology comes from its coalescing of intellects as a multifaceted ground that merges chemistry, bioengineering, biology and medicine. This technology instigates the imagination and its successful implications, but not all visions of the upcoming future are pleasant. Numerous scientists are seriously concerned regarding it and are investigating to insure that the outcomes of nanotechnology are safe and positive. The perception of nanoscale devices has guided to the expansion of biodegradable self-assembled nanoparticles, which are being engineered for the targeted delivery of anticancer drugs and imaging contrast agents [3]. Nanoconstructs can thus serve as customizable, targeted drug delivery vehicles proficient enough in transporting large doses of chemotherapeutic agents or therapeutic genes into malignant cells while not hampering healthy cells [4-13]. The capability to image cellular migration in vivo could be of utmost benefit for unveiling inflammation, tumors, immune response, and effects of stem cell therapy. Advances in nanotechnology driven fields assure improvement in the survival of cancer patients, and will direct to personalized oncology following which cancer detection, diagnosis, and therapy are customized to each individual's tumor molecular profile and also for predictive oncology by employing genetic and molecular markers to envisage disease development, progression, and clinical outcomes. This review eyes on the potential of nanomedicine particularly in developing novel diagnostic and screening techniques and enabling targeted delivery of therapeutic agents.

2. Drug Delivery Systems

2.1 Liposomal delivery systems

Liposomes are self-assembling spherical particles with closed bilayer membranes of water insoluble polar lipids that can be utilized to encapsulate biomolecules and drugs of importance for

targeted delivery while shielding their bioactivity. It may circulate in the bloodstream for prolonged time as compared to a non-liposomal drug which helps in an extended healing process. They were earlier employed as enzyme carriers in lysosomal storage disease and further on utilized in a variety of encapsulated drugs such as antineoplastic agents, antimicrobial compounds, immunomodulators, anti-inflammatory agents, cardiovascular drugs, etc. [14–20]. Recent implications of successful liposomal formulations comprises of doxorubicin (Doxil®), daunorubicin (Daunoxome®), cytarabine (Depocyt®), Myocet®) and vincristine (ONCO-TCS®) and have shown tremendous potential in cancer abatement [21-30]. Instead of its promising ventures, liposomal drug delivery system still needs some advancement like shelf stability, possible suitability for oral administration routes, low loading efficiency, sound control of drug release, inhibition of drug degradation possibility inside the liposome, conquering the difficulty of encapsulating hydrophobic drugs, and bioavailability issues in vivo [31]. Possible expansion in this arena are "stealth liposomes" by coalescing PEG, gangliosides, sialic acid derivatives, hydrophilic synthetic polymers, and other suitable molecules to the surface of the lipid bilayer, which in turn results in increased hydrophilicity, prolonged plasma circulation times as well as site-specificity [32–34].

2.2 Particle carrier systems

Particle based systems have been devised with the notion of enhancing drug bioavailability at target sites, shielding drugs from degradation, and aiding drug absorption as well as diffusion across membranes. Size of particle carriers is one of the most significant aspects which can influence the biodistribution of the resulting vehicle to a great extent. Three types of particles are most evident and they are as follows: (i) macroparticles (50–200 μm), (ii) microparticles (1–50 μm) and (iii) nanoparticles (10–1000 nm). Macroparticles do not go into the capillaries; they are lodged at the arteriole level after administration, and can endow with sustained and slow release of drug to the surrounding tissue while protecting it from biodegradation. Here polymer pore size, swelling properties, and degradation rate can successfully personalize the release rate. Besides all the positive sides, they have shown their inability to enter capillaries and their fast clearance by the reticuloendothelial system (RES). Birrenbach et al, 1976 [35] have devised the initial report on preparation and characterization of polymeric nanoparticles and since then an array of research ventures flourished. The characteristics viz., size distribution, surface charge, biocompatibility, biodegradation behavior, and availability of functional groups for conjugation are essential to the final accomplishment of the delivery vehicle.

High molecular weight polymeric nanoparticles in the range of 110–140 nm, may yield in optimized biodistribution, augmented circulation time, and maximized uptake by target sites. Dextran or PEG coat impart stealth properties to nanoparticles and thereby decrease particle surface charge and bring about extended circulation times. Whereas hydrophilic ligands like chitosan, heparin, and other polysaccharides can improve accumulation at desired tumor loci [36-38]. On the other hand, polymer characteristics also mediates drug release at the target site and that can take place by one of the following three approaches: diffusion of the drug content from hydrated particles, enzymatic degradation of the polymer network, or cleavage of the drug after hydration of the particles. A vast range of natural polymers such as albumin, gelatin, chitosan, and heparin; and synthetic polymers such as poly(amino acids), poly(alkyl-cyano acrylates), poly(esters), poly(orthoesters), poly(urethanes) and poly(acrylamides) put forward successfully in nanoparticle drug carrier design and alleviates delivery of small drugs, oligonucleotides, DNA, and proteins [39-52]. Suitable biodegradability and biocompatibility properties have raised the importance of chitosan, poly(lactic-glycolic acid) (PLGA) (Figure 1), and poly(lactic acid) (PLA) in biomedicine [53-76]. In spite of their several positive sides, polymer nanoparticles also possess a few negative ones, e.g., toxicity of preparation solvents, acidity of degradation byproducts, drug release aspects and control over their size in comparison to liposome.

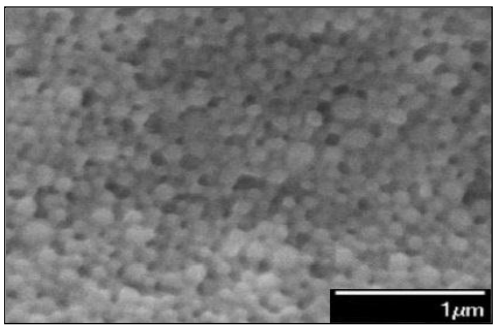

Figure 1: SEM image of PLGA nanoparticles concurrently loaded with indocyanine green and doxorubicin.

2.3 Targeted nanoformulations

Nanoparticles can be targeted to tumor sites either by passive or active manner. Larger pore sizes of blood vessels approaching tumor tissues result in enhanced permeability and retention effect (EPR) of nanoparticle delivered drugs that in turn decrease systemic toxicity. Several aspects are involved in successful optimization of passive targeting for instance parent polymer molecular weight, particle surface charge and hydrophobicity, immunogenicity, tumor characteristics, etc. Neutrally charged particle (average diameter of 10–100 nm, and molecular weights around 30-800 kDa) is the latest venture offering prolonged circulation time [77-80].

Surface decorated (small ligands, antibodies, or biomarkers) nanoparticles can actively direct itself towards specific overexpressed molecular targets on tumor cells followed by the internalization via receptor-mediated endocytosis/phagocytosis and thereby can overcome low tumor specificity [81]. Up to now, several mAbs-based therapies have been implied in targeting disease processes, comprising formulations of trastuzumab [82], cetuximab [83], rituximab [84], and bevacizumab [85]. Aptamers are one of the other choices which are oligonucleic acids with high specificity, small size, and reduced immunogenicity, albeit at high production costs [86-90]. Finally, numerous biomarkers have also been recognized as possible targets of antitumor drugs, including the transferrin receptor, Epidermal Growth Factor Receptor (EGFR), folate receptor, and Human Epidermal Receptor 2 (HER-2) [91-94].

2.4 Combinational delivery systems

Combination of therapeutic agents into a delivery vehicle may comprise delivery of multiple chemotherapeutic drugs [95-102], codelivery of chemotherapy and antiangiogenic agents [103-107], co-delivery of drugs and genes [108-110], and co-delivery of drugs and si-RNA [111-116] and may augment the efficiency of cancer treatment.

3. Biomarkers

Cancer biomarkers such as altered or mutant genes, RNAs, proteins, lipids, carbohydrates and small metabolite molecules are recent potential approaches for the detection of early-stage malignancy that in turn can be correlated with a biological behavior [117]. Molecular profiling through gene expression patterns can reveal the molecular signature of each tumor and provides novel insights into tumor pathology [118-122]. Currently, proteomic approaches as well as combinatorial approaches like cDNA microarrays with tissue microarrays have also been employed for biomarker (HER2/neu, p504S, hepsin, Pim-1, protease/KLK4, prostein, EHZ 2, GSTP1, and STEAP) and immunohistochemical studies (Dako's HercepTest™, Ventana's Pathway™) [123-130]. Instead of their restricted use, clinically proven Trastuzumab (Herceptin™), Gefitinib (Iressa™), Erlotinib (Tarceva™) possess the characteristics in selective targeting of the mutant proteins in malignant cells. The progress of new noninvasive tumor imaging in amalgamation with biomarker targeted imaging contrast agents has sound prospects nowadays for timely detection of cancer and in unveiling the condition of expression of biomarker genes.

4. Multifunctional theranostic systems

Nanosize platforms aid an opportunity for advances in nanoparticle-based theranostic systems which in turn are employed in cancer diagnostics following their versatility, size, and physicochemical characteristics. Nanomaterials can be functionalized with the form of sensors as magnetic nanoparticles, gold nanoparticles, gold nanorods, silica nanoparticles, carbon nanotubes, quantum dots, dendrimers etc. Diverse nanomaterials are portrayed in the subsequent sections highlighting on multifunctional particles.

4.1 Magnetic nanoparticles

Magnetic nanoparticles (MNPs) provide unique theranostic advantages and are utilized for different purposes, such as imaging, cell labeling, drug delivery, gene delivery (Figure 2) and hyperthermia [131-137]. Iron oxide nanoparticles (IONPs), are nanocrystals made from magnetite or hematite and they are popular in following ways: a) IONPs can shorten T2 relaxation time resulting in hypointense images to examine small pathological changes and drug delivery in vivo, b) possess a large surface area for carrying various biomolecules and drugs, c) offer imaging/therapy dual roles in cancer treatment, d) biologically safe as they are degraded and metabolized into the serum Fe pool to form hemoglobin or to go into other metabolic processes [138-140]. Nasongkla et al., 2006 and Yu et al., 2008 have reported the IONP-doxorubicin (DOX)-cRGD micelles and DOX-anti-biofouling polymer coated IONPs based theranostics respectively that can be employed as MR imaging agents and as drug delivery vehicles for upcoming cancer diagnosis and therapy [141, 142]. Next, Cheng et al. 2009 stated porous hollow IONPs as a cisplatin delivery vehicle for target-specific therapeutic applications [143]. A landmark effort documented by Medarova et al., 2007; multifunctional IONPs for

simultaneous in vivo imaging and siRNA delivery into tumors have been devised [144, 145]. Recently, Choi et al., 2012 have demonstrated a theranostic application using IONPs coated with human serum albumin (HSA), which has been considered a biocompatible matrix material for chemotherapeutics, photosensitizers and NPs [146-151]. They also have established that alkylated amphiphilic polymer polyethylenimine (PEI) is capable to encapsulate single or multiple IONPs and form stable composites with sound magnetic properties and biocompatibility in aqueous milieu [152–154].

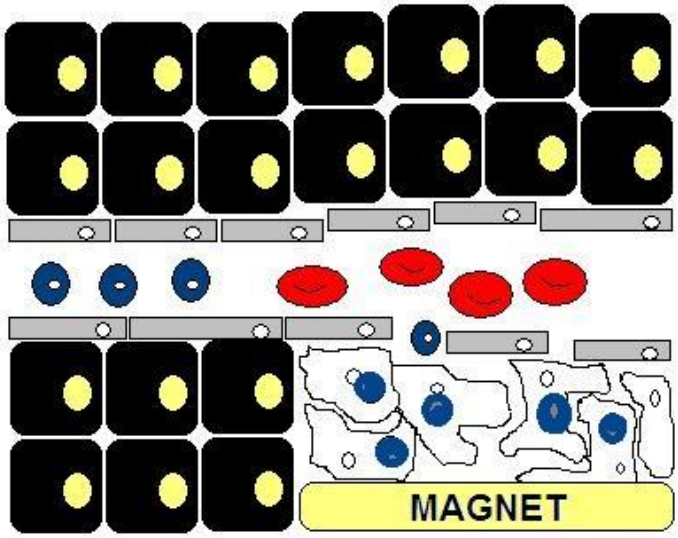

Figure 2: Schematic diagram showing nanoparticle accumulation in tumor cells mediated by magnetically steered gene delivery.

4.2 Gold nanoparticles

Gold nanoparticles (AuNPs) are extensively introspected following their remarkable chemical and optical properties (due to localized surface plasmon resonance), together with ease of conjugation, robust synthesis techniques, low toxicity, and tunable absorption within the near infrared spectral range (Figure 3) [155- 166]. In one recent study, PEG—DTTC—AuNPs in combination gave intense Raman signal at 785 nm and in addition cell viability remained high 24 h post-treatment with it. This supports the utility of AuNPs to study the in vivo fate in the deep tissues of mice [167]. On the other hand, cellular uptake and localization of AuNPs capped with chitosan or branched PEI can be efficiently tracked by Dark field microscopy and surface enhanced Raman scattering (SERS) [168]. Huschka et al., reported that the incubation of serum supported H1299 cell line with AuNS—dsDNA—DAPI complexes result in absorbance and scattering of light by AuNS through darkfield and brightfield microscopy [169]. Same lab has reported the nanoshell-poly-L-lysine-ssDNA (NS-PLL-ssDNA) incubation with H1299 cells and cellular uptake was further confirmed by using darkfield microscopy, fluorescent microscopy, and inductively coupled mass spectrometry [170]. Besides the above implications, the gene silencing efficacy of gold nanoparticle conjugates with microRNA via thiol bonds is also well evident [171]. Gold nanorods have also been utilized to transfect human macrophage cells and deliver siRNA to reduce galectin-1 expression and successive reduction in HIV-1 infection in case of methamphetamine users [172].

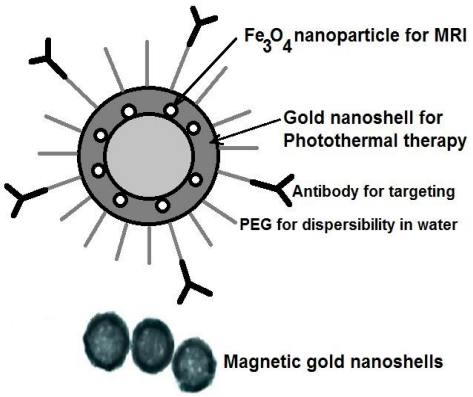

Figure 3: Schematic diagram and TEM image of the magnetic gold nanoshells (Mag-GNS).

4.3 Silica nanoparticles

Silica nanoparticles (SNPs) are robust, bio-inert and easy to control in size and morphology following that they have been used as theranostic nanocarriers to deliver imaging agents and therapeutic molecules to the target site [173, 174]. For example, the hydrophobic photosensitizer DHP-loaded SNPs (DHP-SNPs) exhibited intense fluorescence signals in aqueous medium, allowing for fluorescence bioimaging in cancer theranostics [175]. Particularly, mesoporous silica nanoparticles (MSNPs) have been chosen as a well-accepted nanoplatform for drug delivery and bioimaging applications [176, 177]. Still, the theranostic SNPs are at the nascent stage of improvement, and most studies are limited to in vitro tests whereas lacks information on in vivo biodistribution, toxicity or pharmacokinetics.

4.4 Quantum Dots

Quantum dots (QDs) are semiconductor nanocrystals that in recent years have found useful implication in imaging and diagnostics (Figure 4). They generally range from 2 to 10 nm in diameter and are made of elements from group II–VI or III–V. The most common material being cadmium selenide capped by zinc sulfide (CdSe/ZnS). The size-tunable approach of QD emission wavelengths can help them to fluoresce in between blue and infrared depending on their size after excitation with UV light. The budding potential of QDs for screening cancer markers in classifying tissue biopsies and as high resolution contrast agents for small tumor imaging was only realized in recent times, despite their expansion for electronics and optics two decades ago. Present research inclinations comprise surface amendment, intracellular delivery of therapeutic agents, spatiotemporal imaging, and assessment of toxicity. Bawendi and coworkers (1993) have developed the commonly used method for QDs synthesis and subtle variations are still followed [178- 186]. QDs can be regarded as potential gene delivery systems as cells transfected with QDs and siRNA combination underwent ~90% gene knockdown, whereas siRNA alone underwent only ~20—30% gene knockdown [187]. In addition, F3 peptides can be employed as targeting moieties for improving systemic delivery of siRNA decorated QDs [188].

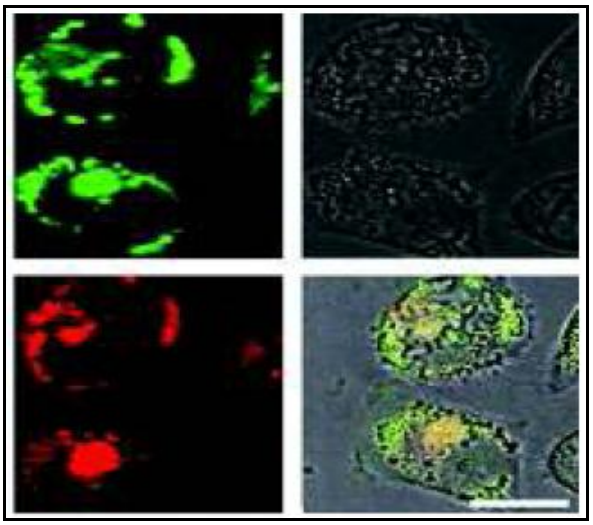

Figure 4: HeLa cells while transfected with CdSe/ZnSe QD/siRNA complexes showing its migration from cell membrane into the cell cytoplasm at 5 h. Here, green fluorescence symbolizes siRNA and red fluorescence represents QDs (J.M. Li et al., Biomaterials 32 (2011) 7978).

In another report, thiol modified RGD and HIV-Tat peptides were coalesced to CdSe/CdS/ZnS QDs with the intention for brain tumor specific targeting [189]. Next, CdTe QDs have also been tried in combination with anti-survivin ASON (a 20mer single stranded DNA) to determine cellular uptake mechanisms and the site of activity [190]. Others have used chitosan coated QDs or different cationic polymers to accomplish efficient cellular transfection and gene knockdown with low cytotoxicity [191-193]. Recently, fluorescent resonance energy transfer (FRET) has been used to collect information regarding spatial conformation of QDs and siRNA or DNA [194-198]. Right now, the trial of QDs is restricted to in vitro and animal studies following the toxicity concerns of cadmium. Near future researchers are trying to produce novel generation of QDs with less amount of cadmium or devoid of cadmium for potential applications in human.

4.5 Carbon nanotubes

Carbon nanotubes (CNTs) were discovered in the late 1980s and are composed of carbon atoms arranged in hexagonal networks that are approximately 1 nm in diameter and 1–100 μm in length [199,

200]. They are single walled (SWCNTs) or multi-walled (MWCNTs), possess large electrical and thermal conductivities, and can be employed in multidimensional approaches, comprising photoacoustic imaging, biosensing as well as cancer cell detection, drug delivery, and photo-thermal therapy [201- 203]. SWCNTs are made up of a single rolled up layer of a graphene sheet, whereas MWCNTs are of multiple rolled layers (concentric tubes of SWCNTs) of graphene. Commonly, covalently conjugated drug molecules like paclitaxel and cisplatin are coupled to the functional groups on the CNTs surface or to the polymer coating of CNTs via cleavable bonds [204, 205]. Upon PEGylated on its surface, CNTs acquire numerous significant properties like high solubility and stability, biocompatibility, and prolonged blood circulation time [206-208]. Next, localized explosions of CNTs by exposing them to a 800-nm laser (50–200 mW/cm2 intensities) can popularize them to be utilized as localized "nanobombs" to destroy cancer cells [209]. They were also successfully employed as carriers for imaging and therapeutic agent delivery. For example, the biodistribution of radio-labeled nanotubes was explored in mice by in vivo positron emission tomography (PET), ex vivo biodistribution and Raman spectroscopy [210-212]. In a promising venture, nanotubes can potentially be used as vehicles for delivery of siRNA in tumor cells for successive release of the cargo to initiate RNA interference on target gene expression [213]. Finally, dual application of intravenously-injected SWCNTs as photoluminescent agents has also been reported for in vivo tumor imaging as well as NIR absorbers for photothermal therapy [214].

4.6 Dendrimers

Dendrimers are repeatedly branched synthetic polymers that are normally 2–10 nm in diameter, with approximately spherical shapes including a large surface area for functionalization with varied targeting and task-specific moieties. Three-dimensional polyamindoamine (PAMAM) dendrimers were first synthesized dendrimers in the 1980's containing tertiary amines and amide linkages [215]. They have been utilized in imaging applications, boron neutron capture therapy, photodynamic therapy, as well as in drug delivery systems [216]. Following their potentiality as Dendrimer based MRI imaging agents (e.g. Gadomer series), Bayer Schering Pharma AG has selected it for clinical trial for possible future implications [217]. Lee et al., 2006 contributed in this area by conjugation of dendrimer branches with polyethylene oxide (PEO) that resulted in their prolonged blood circulation times creating potential stealth delivery platforms [218]. PEG can also be used for the same purpose. An ethylenediamine core polyamido-amine (PAMAM) generation 5 dendrimer that was covalently coalesced to folic acid, fluorescein, and methotrexate, has the prospect to be used for targeting, imaging and intracellular drug delivery [219]. Next, another fifth generation PAMAM dendrimer conjugated to fluorescein isothiocyanate and recombinant Fibroblast Growth Factor-1 was fabricated to track cell targeting and cellular internalization [220]. Furthermore, a multifunctional dendrimer conjugated with fluorescein isothiocyanate, folic acid, and paclitaxel was also synthesized having similar intention [221]. Beside their use as carriers and imaging aid, they are now being evaluated as therapeutic agents (microbicide potential) in clinical trials, viz., anionic functionalized poly-L-lysine dendrimer formulation Vivagel® [222].

5. Conclusions

Nanoformulations has grown to be a flourishing expertise for tailored medicine in which cancer detection, diagnosis, and therapy are customized to each individual’s tumor molecular profile and for predictive oncology in which molecular markers are utilized in anticipation of disease development, progression, and clinical outcomes. The versatility of these so called "smart particles” helped us to overcome the highly invasive nature of tumor cells and the successive side effects and toxicity to healthy cells, which is well evident in case of general cancer treatment options (surgery, radiation, and earlier chemotherapeutic approaches). They can be effectively functionalized to reduce rejection by the immune system and prolonged circulation times, and can be potentially aimed to particular cells by the decoration of surface ligands that prone towards definite receptors. This in turn permits improved accumulation at tumor sites and sustained controllable discharge of therapeutic agents or be employed for additional therapy modalities like hyperthermia. It is of utmost importance to explore nanoparticle distribution, metabolism, excretion, pharmacodynamics, and long-term toxicity in vivo to observe effects in patients and to assess concerns involved in manufacturing and disposal. Besides this, multifunctional theranostic nanoplatforms have provided favorable approaches to deliver the synergistic effect on cancer theranostics like image-guided therapeutics. The final objective will be to increase the diagnostic information and therapeutic efficacy, decrease the time span for early diagnosis, and minimizing the invasiveness. In order to accomplish this progress it requires further exploration and multifaceted cooperation amongst clinicians, biologists, engineers, and material scientists that in turn can assure the long-term safety of nanomaterials.

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